Available online at www.sciencedirect.com

ELSEVIER

Tetrahedron Letters 47 (2006) 6255–6258

Tetrahedron Letters

Iron-catalyzed allylation of ketones

Muriel Durandetti* and Jacques Périchon

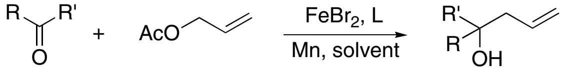
Laboratoire d'Electrochimie, Catalyse et Synthèse Organique, UMR 7582 CNRS-Université Paris 12 Val de Marne,
2 rue Henri-Dunant, 94320 Thiais, France

Received 12 May 2006; revised 22 June 2006; accepted 26 June 2006
Available online 14 July 2006

Abstract—Allylation of ketones has been efficiently performed using iron-complex catalysis and led to homoallylic alcohols in high yields.

The allylation of carbonyl compounds by means of allylic metal reagents is a very important class of C–C bond forming reactions, since it gives rise to synthetically useful homoallylic alcohols.[1] These compounds can be easily converted to various building blocks useful for the synthesis of natural products.[2] Different methods of allylation have been developed mainly based on the nucleophilic character of the allylmetal obtained from allyl bromides and metallic species (metal = Li,[3] Mg,[4] Al,[5] Zn,[6] Ni,[7] etc.). More recently allylic organometallic compounds, such as allyl-chromium,[8] -indium,[9] -manganese,[10] -silane,[11] -boronate,[12] -stannane,[13] etc., have been examined. Allylation of carbonyl compounds from allylic acetate requires the use of palladium as catalyst, in addition to another metal or a reducing salt.[14] In most cases, only aldehydes are reactive. The allylation of ketones seems more difficult, except in the presence of SmI_2.[15] Allylstannane or allylsilane also permits the allylation of ketones, and enantioselective approaches are even known in this field.[16] In our laboratory, we have shown that a cobalt-catalyzed coupling reaction of allyl acetates with carbonyl compounds using zinc dust as reducing metal leads to homoallylic alcohols.[17] Another access to allylic anions is their electrochemical generation, for example using catalytic amount of tin and allyl bromide.[18] We already described some electrochemical processes for the synthesis of homoallylic alcohols.[19] With the intention of having a less toxic process, iron species have been added to the relatively large list of catalysts known to carry out allylation reactions.[20] Allylation of aldehydes with allyl trimethylsilane occurs also with $FeCl_3$.[20b] In the same time, we initiated a work investigating iron catalysis[21] because of the abundance of the metal, its low toxicity, and its cheap price. We have recently reported iron-catalyzed electrochemical allylation reactions of carbonyl compounds.[22] In this reaction homoallyl alcohols are prepared from aldehydes or ketones and allylic acetates, using an electrochemical process catalyzed by iron complexes. The reaction proved to be highly regioselective, affording almost exclusively branched homoallyl alcohols. However, electrochemical reactions are often considered as being less scalable than conventional classical methods. Thus, electrochemical processes are infrequently applied in industrial scale. We have then reported a chemical method for an iron Reformatsky type reaction, using $FeBr_2$ as catalyst in the presence of an appropriate reducing metal.[23] We intended to show that this method can be suitable for the activation of allyl acetates. We present in this paper the investigation of iron-catalyzed coupling reaction from allyl acetates with ketones (Scheme 1), leading to homoallylic alcohols.

We first conducted a series of experiments with allyl acetate and ketones under the reaction conditions previously used for the Reformatsky reaction[23]



Scheme 1. The allylation reaction.

---

* Corresponding author at present address: Laboratoire des Fonctions Azotées & Oxygénées Complexes de L'IRCOF, UMR CNRS 6014, Université et INSA de Rouen, 76821 Mont Saint-Aignan Cedex, France. Tel.: +33 (0)2 35 52 24 37; fax: +33 (0)2 35 52 29 71; e-mail: muriel.durandetti@univ-rouen.fr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.134

(i.e., $FeBr_2$bipy (0.25 equiv) as catalyst in DMF or $FeBr_2$ (0.15 equiv) without ligand in acetonitrile). Manganese metal was used as reducing metal of iron salts. We observed at first that the reaction is best performed at 80 °C, and that chemical yields are better using 25% of $FeBr_2$bipy in DMF, than $FeBr_2$ in acetonitrile. However, even at this temperature, chemical yields of homoallylic alcohols are low: about 30–40%, whatever the method used, the amount of iron salts or the ketones. The reaction appears to stop, since carbonyl compounds are recovered at the end (see the kinetics in Fig. 1). We tried then to optimize the reaction conditions using $FeBr_2$bipy in DMF (Scheme 2).

In all cases, the reactions seem to be blocked at one stage (Table 1). Ketones and allyl acetates are no more consumed. We supposed then a complexation step of iron salts by acetate ions generated during the process. However, we found that the yields could not be increased by the use of larger amounts of the iron catalyst (even with 1 equiv), or with addition of 1 or 2 equiv of Me_3SiCl, even if the reaction occurs quickly in this case (Table 1, entries 1 and 2). Moreover, when we ran the reaction without carbonyl compounds, we obtained the quantitative formation of hexadiene, thus confirming the formation of the π-allyl-iron complex. As allyl acetate is totally consumed, nothing prevents the reaction to go at the end. We then tried to add another salt like LiCl or $ZnBr_2$. Chemical yields increased only in the presence of $ZnBr_2$. As shown in Figure 1, best results are obtained with 50 mol % of $ZnBr_2$. We could suppose that the π-allyl-iron, generated during the process, reacted with $ZnBr_2$ to lead a π-allyl-zinc species.

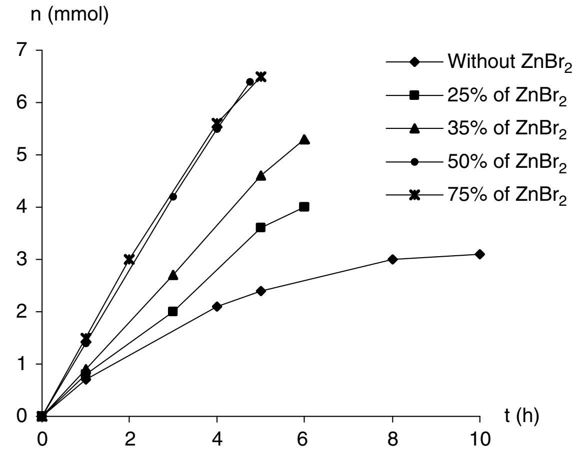
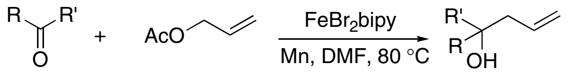
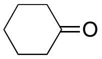
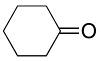
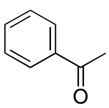
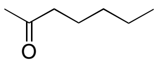


Figure 1. Evolution of the cross-coupling product between acetophenone and allylOAc as a function of $ZnBr_2$.



Scheme 2. Allylation catalyzed by $FeBr_2$bipy in DMF as solvent.

Table 1. Allylation of ketones using $FeBr_2$bipy as catalyst

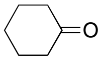
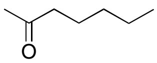
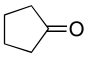
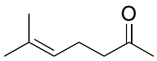
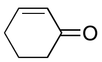
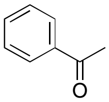
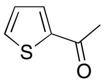
Entry	Ketones	Yields (%) of coupling product[a]
1		40[b]
2		43[c]
3		39
4		31

[a] Isolated yields, based on initial ketone.
[b] Reaction time: 30 h.
[c] Reaction conducted with 1 equiv of Me_3SiCl; reaction time: 3 h.

After optimization the best conditions were found to be 0.25 equiv of $FeBr_2$bipy in the presence of 0.5 equiv of $ZnBr_2$, providing 50 to 80% of homoallylic alcohols in 5 h approximatively as shown in Table 2.[25] Chemical yields are moderate to good. Therefore, the use of iron in the presence of zinc salts allows the coupling between allyl acetate and ketones. This method is efficient with aliphatic, cyclic, as well as aromatic ketones (Table 2). No conjugated addition was observed with cyclohexenone, thus indicating that the reaction is regiospecific (Table 2, entry 5).

We then tried to realize the reaction between cyclohexanone and allyl acetate under the same conditions but without $FeBr_2$bipy as catalyst. In this case, no coupling product was obtained even after five days. The iron catalysis is necessary to obtain the coupling product.

Table 2. Allylation of ketones using $FeBr_2$bipy as catalyst, in the presence of $ZnBr_2$

Entry	Ketones	Yields (%) of coupling product[a]
1		79
2		61
3		51
4		41[b]
5		71
6		68
7		53

[a] Isolated yields, based on initial ketone.
[b] 50% of ketone is recovered.

The chemistry of allylic compounds also includes the additional regiochemical aspect. So we ran a series of experiments with the same experimental procedure, using crotyl acetate (or its allylic isomer), instead of allyl acetate. Reactions involving allylic derivatives generally give two isomeric products due to allylic transposition (Scheme 3).

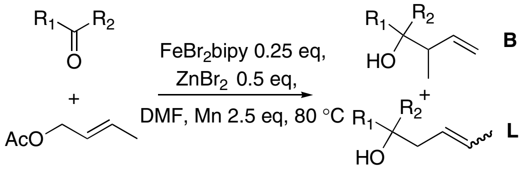
The ratio of branched to linear alcohol (**B**/**L**) is known to depend mainly on the nature of the metal in the organometallic reagent.[1a,24] In our hands, the major product formed in these reactions is the branched one **B**, with an approximate ratio **B**/**L** of 9/1 (Table 3). However, the regioselectivity decreased with reaction time (Table 3, entries 5 and 6) and isomerization was complete after a day (Table 3, entry 3).

The yields are moderate to good and do not seem to greatly depend on the nature of the butenyl acetate (crotyl or its isomer) (Table 3, entries 1 and 2). So, crotyl acetate and 1-methyl prop-2-enyl acetate are as efficient in this coupling reaction: same yield, and same **B**/**L** ratio.

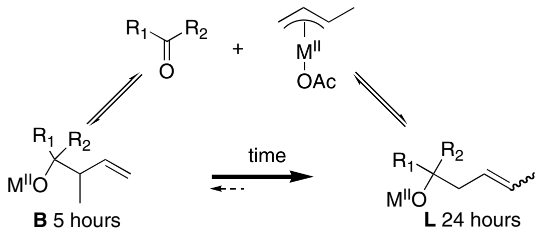
In the case of dissymetric carbonyl compounds (Table 3, entries 5 and 7), we obtained the coupling product, as two couples of diastereoisomers, with a very moderate diastereoselectivity. The ratio *anti*/*syn* is 55/45.

Even if the reaction is regioselective in favor of the branched product, the coupling product isomerizes into the linear coupling product if the alkoxide is left to stir after the end of the reaction (Table 3, entry 3). We have access to both isomers, depending on the reaction time. If the crude product is hydrolyzed immediately after the end of the reaction (ca. 5 h), the branched product is obtained as the main product. Instead, if the desired product is the linear isomer, we just have to wait 24 h before quenching the reaction. An equilibrium should exist between the kinetic and the thermodynamic isomers, probably initiated by a reversible reaction of allylation (Scheme 4).

We supposed that the reversibility is due to the presence of zinc in the solution. If the reaction is run with crotyl acetate without $ZnBr_2$, homoallylic alcohols are obtained in poor yields (ca. 30%) with a **B**/**L** ratio of

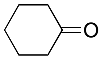
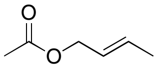
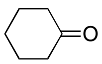
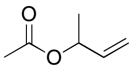
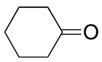
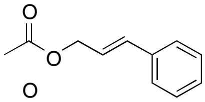
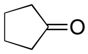
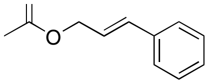
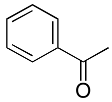
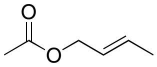
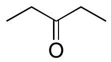
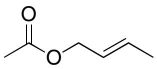
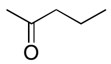
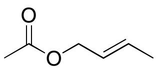


Scheme 3. Regioselectivity of the iron-catalyzed addition of crotyl acetate to ketones.



Scheme 4. Equilibrium between homoallylic alkoxides.

Table 3. Regioselectivity in the iron allylation reaction

Entry	Ketones	Allylic compounds	Yields[a] (%)	Ratio **B**/**L**
1			80	95/5
2			77	94/6
3			86	82/18[b]
4			41	90/10
5			51[c]	80/20[d]
6			69	75/25[d]
7			69[c]	87/13

[a] Isolated yields, based on initial ketone.

[b] Ratio **B**/**L** = 20/80 if the alkoxide is hydrolyzed after only 24 h.

[c] Product **B**: *anti*/*syn*: 55/45.

[d] Reaction time is longer than 5 h, so ratio **B**/**L** = 95/5 after 3 h and 80/20 after 6 h.

95/5 even after 12 h. The reversibility of allylation using allylic organozinc reagent has already been reported by Miginiac et al.,[6a,b] who mentioned that homoallylic alcohol are obtained initially with a ratio **B**/**L** of 50/50, and of 0/100 after 12 h.

In conclusion, we have reported in this paper an original method of efficient addition of allylic acetates to ketones, enabling the preparation of valuable target molecules: homoallylic alcohols. The method is also very easy, cheap, and low toxic, compared to the other methods described in the literature, where palladium complexes, in the presence of another reducing salt, must be used to activate allyl acetate. The reduction of Fe^{II} by manganese metal probably leads to Fe^0, which is stabilized by 2,2′-bipyridine. Reactions are regioselective: the branched product **B** is the major product, but the process permits the obtention of the linear isomer.

References and notes

1. Reviews: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293; (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793.
2. (a) Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. B. *Tetrahedron Lett.* **2000**, *41*, 583–586; (b) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19–20.
3. Alonso, E.; Guijarro, D.; Ramon, D. J.; Yus, M. *Tetrahedron* **1999**, *55*, 11027–11038.
4. (a) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18; (b) Yamamoto, Y.; Maruyama, K. *J. Org. Chem.* **1983**, *48*, 1564–1565.
5. Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1–44.
6. (a) Miginiac, P.; Bouchoule, C. *Bull. Chim. Soc. Fr.* **1968**, 4675–4676; (b) Barbot, F.; Miginiac, P. *J. Organomet. Chem.* **1977**, *132*, 445–454; (c) Ranu, B. C.; Majee, A.; Das, A. R. *Tetrahedron Lett.* **1995**, *36*, 4885–4888; (d) Sklute, G.; Marek, I. *J. Am. Chem. Soc.* **2006**, *128*, 4642–4649.
7. Hegedus, L. S.; Wagner, S. D.; Waterman, E. L.; Siirala-Hansen, K. *J. Org. Chem.* **1975**, *40*, 593–598.
8. (a) Nowotny, S.; Tucker, C. E.; Jubert, C.; Knochel, P. *J. Org. Chem.* **1995**, *60*, 2762–2772; (b) Baati, R.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **2000**, *65*, 1235–1238.
9. (a) Khan, F. A.; Prabhudas, B. *Tetrahedron* **2000**, *56*, 7595–7599; (b) Lombardo, M.; Girotti, R.; Morganti, S.; Trombini, C. *Org. Lett.* **2001**, *3*, 2981–2983; (c) Hirashita, T.; Kambe, S.; Tsuji, H.; Omori, H.; Araki, S. *J. Org. Chem.* **2004**, *69*, 5054–5059.
10. (a) Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373; (b) Fürstner, A.; Brunner, H. *Tetrahedron Lett.* **1996**, *37*, 7009–7012; (c) Kakiya, H.; Nishimae, S.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 8807.
11. (a) Davis, A. P.; Jaspars, M. *J. Chem. Soc. Perkin Trans.* **1992**, 2111–2118; (b) Yadav, J. S.; Chand, P. K.; Anjaneyulu, S. *Tetrahedron Lett.* **2002**, *43*, 3783–3784.
12. (a) Arnauld, T.; Barrett, A. G. M.; Seifried, R. *Tetrahedron Lett.* **2001**, *42*, 7899–7901; (b) Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* **2002**, *58*, 7381–7389.
13. (a) Kamble, R. M.; Singh, V. K. *Tetrahedron Lett.* **2001**, *42*, 7525–7526; (b) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191–193.
14. (a) Masuyama, Y.; Kinugawa, N.; Kurusu, Y. *J. Org. Chem.* **1987**, *52*, 3704–3706; (b) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *2*, 847–849.
15. Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 1195.
16. (a) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061; (b) Tietze, L. F.; Volkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schafer, M. *Chem. Eur. J.* **2001**, *7*, 1304–1308; (c) Pignataro, L.; Benaglia, M.; Annunziata, R.; Cinquiti, M.; Cozzi, F. *J. Org. Chem.* **2006**, *71*, 1458; (d) Denmark, S. E.; Fu, J.; Coe, D. M.; Su, X.; Pratt, N. E.; Griegel, B. D. *J. Org. Chem.* **2006**, *71*, 1513; (e) Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523.
17. Gomes, P.; Gosmini, C.; Périchon, J. *Synthesis* **2003**, 1909–1915.
18. Torii, S.; Uneyama, K.; Matsuda, H. *Tetrahedron Lett.* **1984**, *25*, 6017–6020.
19. (a) Durandetti, S.; Sibille, S.; Périchon, J. *J. Org. Chem.* **1989**, *54*, 2198–2204; (b) Rollin, Y.; Derien, S.; Dùnach, E.; Gebehenne, C.; Périchon, J. *Tetrahedron* **1993**, *49*, 7723–7732; (c) Durandetti, M.; Nédelec, J.-Y.; Périchon, J. *Org. Lett.* **2001**, *3*, 2073–2076.
20. (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217; (b) Watahiki, T.; Oriyama, T. *Tetrahedron Lett.* **2002**, *43*, 8959–8962.
21. Durandetti, M.; Meignein, C.; Périchon, J. *Org. Lett.* **2003**, *5*, 317–320.
22. Durandetti, M.; Meignein, C.; Périchon, J. *J. Org. Chem.* **2003**, *68*, 3121–3124.
23. (a) Durandetti, M.; Périchon, J. Patent application, FR 2004–7230; (b) Durandetti, M.; Périchon, J. *Synthesis* **2006**, 1542–1548.
24. Ito, A.; Kishida, M.; Kurusu, Y.; Masuyama, Y. *J. Org. Chem.* **2000**, *65*, 494–498.
25. General procedure for the cross-coupling of allylic acetates with carbonyl compounds: 10 mmol of carbonyl compounds and 13 mmol of allylic acetates were added in a stirred flask under argon at 80 °C with 30 mL of DMF. Then 1.35 g of Mn (25 mmol) is introduced, followed by 1.1 g of $ZnBr_2$ (5 mmol), 0.39 g of 2,2′-bipyridine (2.5 mmol), and 0.54 g of $FeBr_2$ (2.5 mmol) and finally 20 μL of CF_3CO_2H to activate manganese metal. The reaction is conducted at 80 °C and was monitored by GC-analysis and quenched after the carbonyl compounds were consumed (ca. 5 h for the branched product or 24 h for the linear product). The mixture was then hydrolyzed with 1 N HCl and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with water and saturated NaCl solution, dried over $MgSO_4$, and the solvent was evaporated. The oil thus obtained was purified by column chromatography to give the desired compounds.